DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
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STATEMENT OF
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FOOD AND DRUG ADMINISTRATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

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SUBCOMMITTEE ON OVERSIGHT AND

INVESTIGATIONS

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INTRODUCTION

Mr. Chairman and Members of the Subcommittee, I am Andrew C. von Eschenbach, M.D., Commissioner of Food and Drugs at the United States Food and Drug Administration (FDA or the Agency). I am pleased to be joined here today by my Agency colleagues, Ms. Margaret Glavin, Associate Commissioner for Regulatory Affairs, and Ms. Deborah Autor, Director, Center for Drug Evaluation and Research (CDER) Office of Compliance. Thank you for the opportunity to discuss the important issues relating to FDA's foreign drug inspection program.

FDA-regulated products include human and animal drugs, vaccines and other biological products, food and animal feed, cosmetics, and medical devices. FDA's regulation of these products is considered the "gold-standard" around the world and our goal is not only to maintain that standard but to continuously strive for improvement. Yet, in keeping this commitment to the American consumer, we do face significant challenges. We recognize that the world is evolving and our local markets now provide products largely from a global marketplace.

FDA is keenly aware that we must systematically assess these global market issues as they relate to drug products and other FDA-regulated products manufactured overseas. Therefore, we are developing comprehensive solutions to face these global challenges.

FDA REGULATION OF FOREIGN-MANUFACTURED DRUGS

FDA's monitoring of foreign-manufactured drugs is based on far more than foreign inspections. To comply with the Food, Drug, and Cosmetic (FD&C) Act, any entity that intends to import

drugs into the U.S. must ensure that the drug meets a number of quality and labeling requirements.

In the FD&C Act, Congress enacted provisions to create a relatively "closed" distribution system for imported drug products to help ensure the domestic supply is safe and effective by limiting the drugs and biologics that may be imported into the U.S. All "new drugs," which includes all finished prescription drug products, must be approved by FDA as safe and effective for their intended use. FDA approvals are manufacturer-specific and product-specific, and include many requirements related to the product, such as manufacturing location, formulation, source and specifications of active ingredients, manufacturing controls, the container/closure system, and labeling. Facilities that manufacture drugs for the U.S. market must meet FDA's current good manufacturing practice (cGMP) requirements.

When an FDA-regulated drug product is offered for import into the U.S., U.S. Customs and Border Protection (CBP) notifies FDA. If the product appears to violate the FD&C Act, FDA will give notice advising its owner or consignee of the violation and the right to provide testimony demonstrating why the article at issue is not violative or to request permission to recondition the product. If the product is ultimately refused admission, it must be destroyed unless exported by the owner or consignee within 90 days from the date of refusal.

FDA performs 100 percent screening of active pharmaceutical ingredients (API) and drug products entering into the U.S. to establish whether, if required, FDA has approved the drug product or the API is consigned to a plant that corresponds with its designated approval in the drug product application. Also, FDA screens whether the manufacturing plant is registered and

the drug is listed. FDA performs surveillance examinations of imported goods to check for compliance with U.S. requirements.

Another key tool is the Import Alert, which signals FDA field personnel to pay special attention to a particular product, manufacturer, shipper and/or importer. FDA issues Import Alerts for Detention Without Physical Exam (DWPE) when we have information that would cause future shipments of a product offered for entry to appear violative within the meaning of section 801 of the FD&C Act. This allows FDA field personnel to detain the product without physical examination, based on the appearance of a violation as documented in the Import Alert. Once FDA detains a product under 801(a) the burden shifts to the importer to demonstrate why, in fact, its product complies with U.S. law. In addition, FDA personnel also perform periodic filer evaluations to ensure import data provided to the Agency are accurate.

U.S. manufacturers also have a responsibility to ensure the safety of foreign-manufactured ingredients used for their finished dosages. U.S. manufacturers of finished dosage drugs that import APIs from abroad are to examine and test ingredients before using them in their drug products under cGMP. FDA may inspect a firm's foreign facilities and/or their domestic facilities to determine if the manufacturing facility meets the Agency's quality standards. In addition, FDA inspections routinely evaluate manufacturers' testing and controls of ingredients and supplies. FDA inspects all API manufacturers for compliance with cGMP prior to the approval of the dosage form's new drug application (NDA), abbreviated new drug application (ANDA), or biological license application (BLA). If during a domestic or foreign inspection, FDA determines that an imported API fails to meet specifications or is manufactured using unsafe practices, an import bulletin can be used to trigger testing of future shipments, or the drug can be subject to automatic detention at the U.S. border.

Foreign Inspections

FDA performs over 200 foreign drug manufacturing inspections per year. Exercising FDA's regulatory authority abroad can be challenging. In some countries, we need authorization from the relevant government to enter and inspect facilities and other countries have travel alerts that require FDA to take special precautions to ensure the safety of our investigators. Many of these firms are motivated to have FDA inspect their facilities because they have an application pending with the Agency that may require a pre-approval inspection.

Foreign inspections are more costly because of travel costs and special needs associated with travel in a foreign country. Foreign drug inspections are typically scheduled for five days. Depending on the product involved, we have scheduled inspections for as short a period as three days for a control testing laboratory, and up to two weeks for a sterile product.

There are approximately 800 FDA investigators trained to conduct foreign inspections in all program areas and 335 specifically for the drug program area. Also, CDER supports these inspections with additional technical experts and trained investigators. FDA typically solicits for volunteers from this specially trained cadre of investigators. The inspections are often conducted by one investigator who will conduct three, five-day inspections consecutively.

FDA foreign investigators are highly experienced and well-equipped. They often have many years of domestic experience and are dedicated to working long hours to accomplish an inspection in the allotted time. Some investigators speak foreign languages. FDA also relies on assistance from the firms' U.S. agents and representatives to translate if needed and help with logistical challenges that arise in traveling to a foreign firm. The investigators travel on official U.S. government passports requiring FDA to notify the U.S. Department of State and relevant

embassies. We are planning to strengthen our collaboration with embassy staff to assure our investigators are well prepared for local conditions.

Drug Ingredient Safety

Foreign activity in drug counterfeiting and contamination is an on-going concern for the U.S. and other nations. Ten years ago, counterfeit glycerin contaminated with diethylene glycol (DEG) killed nearly 100 children in Haiti. Last year in Panama, glycerin contaminated with DEG, traced to China, again caused scores of deaths. Recently, toothpaste imported from China was also found to contain DEG. To minimize the potential of DEG contamination of ingredients in the U.S., the Agency immediately issued guidance alerting drug manufacturers to perform testing for DEG contamination on all shipments of glycerin used in the formulation of drugs. FDA's CDER formed a task force, which developed a series of action items aimed at pro-actively addressing our susceptibility to similar pharmaceutical ingredient contamination and misbranding incidents.

As more pharmaceutical ingredients are sourced from abroad, an increased number of foreign intermediaries become involved in the supply chain. Discussions with the International Pharmaceutical Excipient Council (IPEC-Americas), a trade organization comprised of drug manufacturers and excipient manufacturers and distributors, has echoed our concerns and findings regarding the complexity of global supply chains and the lack of traceability of excipients to their original manufacturers. Pharmaceutical manufacturers can reduce the associated risks by obtaining intelligence about the distribution chains for each imported ingredient by establishing more robust systems and procedures to qualify suppliers of pharmaceutical ingredients and assure the identity and purity of batches of incoming ingredients.

IMPROVING THE OVERSIGHT OF FOREIGN MANUFACTURED DRUGS

Information Technology (IT) Enhancements

Since taking the position as FDA Commissioner, upgrading FDA's IT systems has been one of my top priorities. We expect these improvements will help address the challenges we face in the area of foreign inspections. Logistically, foreign firms are more difficult to track and more challenging to inspect than domestic firms. The data we have regarding foreign firms is not easy to confirm or check for accuracy because we cannot easily gain access to the firms. Foreign firms must register with FDA before shipping to the U.S. Because there is no cost to register, some firms register, but do not actually produce a product or ship products to the U.S, or discontinue shipping without any notice to FDA. The practice of registering without producing or shipping can create uncertainty at any given moment about the precise number of FDA registered firms from which to target inspections, often necessitating secondary data-source checking.

FDA does have the ability to capture the importation of drug products and the manufacturer of those products through its Operational and Administrative System for Import Support (OASIS) system. The information provided by the importer often leads to duplicate entries of manufacturers due to name, configuration, and address changes or does not accurately identify the site-specific manufacturer of the product.

We are working on more effective and efficient solutions to ensure the accuracy and validity of the data in our registration and import IT systems. FDA has set up the Bio-informatics Board (BiB) to address this issue for FDA. The Product Quality subgroup focuses on the issue of establishing accurate information on firms and their products. We are actively seeking other

means to identify duplicate entries, such as those caused by variations of the same name and address (e.g. use of third-party validation of non-confidential business information). Additionally, the Agency's current initiative to implement electronic registration of firms holds promise to redirect our resources from data entry, enabling us to focus instead on quality assurance of the data bases. In addition, the BiB directs the work and approves recommendations set forth by the Business Review Boards (BRBs). BRBs define business processes, driving outcomes enabled by IT services.

The Office of the Chief Information Officer is leading enterprise-wide IT transformation initiatives and establishing an aggressive two-year plan to rebuild FDA's critical IT infrastructure. Several key projects are underway that will sustain the transformation.

- FDA's Decision Support System will be enhanced to boost performance and expand the ability to rapidly access information critical to managing FDA's foreign drug inspection program. OASIS and Field Accomplishments and Compliance Tracking System (FACTS) will be migrated into 21st century database and hardware platforms to enhance critical functionality (target date: February 2008).

- FDA is implementing upgrades to the Agency's IT systems to increase efficiency of import entry review by allowing users to access multiple databases across the Agency under a single sign-on capability. Included systems are Drug Registration and Listing System (DRLS), Document Archiving, Reporting and Regulatory Tracking System, Mission Accomplishments and Regulatory Compliance Service (MARCS), OASIS and FACTS.

- FDA is developing and implementing a firm management and tracking system called Firm Management Services (FMS) that will allow users to input and search for firms in multiple repositories, improving the quality of data received by FDA and enabling the Agency to better screen imported products and identify firms shipping to the U.S. FMS will replace older, less effective technology used by FACTS/OASIS and older components of MARCS's applications.

- FDA is also developing a Firm Finder application to allow users to search firms in multiple repositories from one access point. Identifying and retrieving information about these firms is a key step in the evaluation of imports. Firm finder will use web services to integrate with legacy (FACTS/OASIS) and MARCS's applications.

- FDA is re-engineering MARCS, a major FDA IT program, to integrate and enhance several FDA systems, including OASIS and FACTS, by collecting and processing information obtained by or needed to support FDA field operations.

- FDA is working on FDA's Unified Registration and Listing System (FURLS) to integrate Center for Food Safety and Applied Nutrition, Center for Devices and Radiological Health, CDER, Center for Biologics Evaluation and Research, Center for Veterinary Medicine, registration and listing systems.

- FDA has initiated software development of the Electronic Broker Information Center, a universal data interface application for filers, importers, or consignees to use a secure communication means to submit documents in support of entry review processes, location and availability data, view import entry and FDA line statuses, Notices of FDA Action, and perform firm and product data queries.

- FDA is working with CBP to ensure its planned Automated Commercial Environment (ACE) upgrade, a component of the International Trade Data System (ITDS), will provide real-time data feeds, ensuring that FDA receives all needed data elements electronically while harmonizing and validating information across centers.

- FDA is also engaging in ongoing cleanup of internal data to ensure rapid access to information in support of FDA import safety operations and upgrade of internal systems to synchronize and validate data across centers.

- FDA is developing and testing a system, which will utilize artificial intelligence in conjunction with analytical and inspectional data (foreign and domestic), and multiple data sources to identify products and shipments posing the greatest safety risks. The system is currently being evaluated for seafood products entering in the Port of Los Angeles and if successful will be expanded to other commodities.

- FDA is developing an Import Portal to allow Customs Brokers to more quickly exchange information with Import Reviewers about shipments/entries submitted for FDA review. The target for completion of development of this Import Portal is late FY 2009.

- FDA is making substantial improvements in its IT infrastructure critical to ensuring the exchange of data between its field offices and Headquarters, including CBP as it monitors products entering the U.S. FDA completed the network circuit upgrade in early 2007. The router, server, and Laboratory Storage Area Network (LABSAN) upgrade, installation, and operation lease agreement is in place and will be executed through October 2008. LABSAN is an infrastructure built to manage data and provide effective quality assurance to maintain data credibility and centralized data storage. LABSAN ultimately reduces time spent accessing and analyzing drug import data.

- FDA's Program Quality System is an Agency-wide initiative that encompasses an electronic mechanism for manufacturers' registration and product listings, as well as capturing inspection data from compliance reviews. FDA's Product Quality Business Review Board has completed the second phase of a three-phase project to harmonize the

processes for tracking regulated establishments and their products. Initial planning for this initiative should be completed by the end of December 2007.

International Efforts

FDA has a variety of cooperative relationships with foreign regulators, ranging from cooperation under a Free Trade Agreement, to agency-to-agency Memorandums of Understanding (MOUs), to informal arrangements established by exchanges of letters. A list of FDA's commitments appears on FDA's Office of International Programs, International Arrangements, web page (http://www.fda.gov/oia/default.htm).

FDA exchanges inspectional information with many foreign partners. Our relationships with some of these partners have become quite sophisticated and intense, developing to the point where we are communicating with them on a daily, and sometimes hourly, basis. FDA is currently engaged in the formal assessment of the efficacy of one foreign regulatory agency for more systematic use. Under the MOU between FDA and Swissmedic, the Swiss Agency for Therapeutic Products, technical experts have cooperated for three years on inspection collaboration with a desired endpoint of utilizing each other's inspection reports in making regulatory decisions. Both sides, however, would retain the authority to inspect manufacturers in the other country at any time.

FDA is also in the process of joining the Pharmaceutical Inspection Co-operation Scheme (PIC/S). PIC/S fosters cooperation among pharmaceutical inspection authorities in pharmaceutical good manufacturing practices (GMP), as well as developing and promoting harmonized GMP standards and guidance documents, training competent authorities (in particular inspectors), and assessing and re-assessing inspection authorities. FDA submitted a formal application to join PIC/S in September 2005. Upon acceptance, it will enable the

exchange of inspection reports and other inspection information with regulatory authorities. The PIC/S application process typically takes two years or more.

Another development on this front has been the establishment this year of the European Union (E.U.)-U.S. Bilateral Technical Working Group on Medicines Quality and Manufacturing. This group will have a major focus on utilizing shared resources through information exchange of inspectional data for plants in the U.S. and E.U. Another important planned activity of this group will be to share inspectional information from companies located in countries.

To promote and enhance the safety of all imported products, the President issued an Executive Order on July 18, 2007, that established the Interagency Working Group on Import Safety (Working Group). The Working Group, which includes representatives from 12 Federal departments and agencies, is tasked with reviewing the procedures, regulations, and practices for ensuring imported drugs, food, and other consumer products are safe. Secretary of Health and Human Services (HHS), Michael O. Leavitt, chairs the Working Group and FDA plays a key role. Secretary Leavitt and I traveled extensively throughout the country during the past few months visiting ports of entry and reviewing FDA field operations.

On September 10, 2007, the Working Group provided the President with an initial report on steps to improve import safety. The report, "Protecting American Consumers Every Step of the Way: A Strategic Framework for Continual Improvement in Import Safety," outlines an approach that can build upon existing efforts to improve the safety of imported products, while facilitating trade. It recommends that the Federal government work with the importing community in developing methods to address safety risks over the life cycle of imported

products and focus actions and resources to minimize the likelihood of unsafe products reaching our borders.

On October 1, 2007, the Working Group conducted a public meeting in Washington, D.C., to receive input from stakeholders. By mid-November of this year, an Action Plan based on the Strategic Framework will be provided to the President. The plan will reflect the public comments and recommend specific action steps the Federal government and stakeholders can take to enhance import safety at all levels.

Federal departments and agencies have already begun to implement high-priority recommendations from the interim report. By November 12, 2007, Federal entities that rely on IT systems in their review of imported cargo must develop implementation plans to achieve interoperability of their import data systems with ITDS managed by CBP. This requirement is consistent with the Security and Accountability for Every (SAFE) Port Act of 2006 and will ensure a single-window system for reporting on imports electronically.

The safety of products from China, as well as other trading partners, remains a concern for Secretary Leavitt and I, our staffers, Congress, and American consumers. The recent DEG episode has reinvigorated attention on China's regulation of its finished drug products, APIs, and excipients. We have limited knowledge of the quality of ingredients and products manufactured in China as this fast growing source is just beginning to put in place a national regulatory infrastructure. In the past four years, the number of FDA-registered drug manufacturers in China has at least doubled. The Chinese government is in the process of re-writing its existing cGMP for drugs. Drug manufacturers in China, and some other developing countries, comply with cGMP inconsistently and to varying degrees. Provincial authorities who conduct

inspections of drug manufacturing sites in China are not always equipped with the expertise needed for this complex undertaking.

The Office of Compliance within CDER conducted a series of educational workshops in China in December 2005 and April 2006 on current cGMP, in collaboration with the International Society for Pharmaceutical Engineering and Peking University. The workshops were intended to educate participants on current methods for compliance with cGMP, to ensure effective cGMP programs, and to further the common goals of FDA and providers of quality pharmaceutical products. The workshops were open to any professionals involved in the manufacture, control, and regulation of pharmaceutical products, including process/production engineers, manufacturing personnel, quality assurance/quality control and regulatory affairs professionals, consultants, regulatory investigators and cGMP compliance officials.

With the leadership of Secretary Leavitt, FDA and others within HHS are actively engaged with our Chinese counterparts in negotiating agreements that will include commitments relating to many FDA-regulated products to increase our confidence in the safety of these Chinese products that are exported to the U.S. A delegation of senior HHS and FDA officials are holding a second round of negotiations with senior Chinese officials in the Washington D.C. area. Represented agencies included the Chinese State Food and Drug Administration and the General Administration of Quality Supervision, Inspection and Quarantine. While these two agencies have very different roles, we are optimistic that we will negotiate an agreement with each agency that advances our nation's objectives, although perhaps with different approaches. We are continuing formal negotiations on two agreements, one on the safety of food and feed, and another on the safety of drugs and medical devices. I believe these talks are yielding significant

progress towards achieving two, strong, action-oriented documents, and I look forward to the signature of these documents.

CONCLUSION

Ensuring the safety of the drug products used by American consumers continues to be a top priority for FDA and we are working hard in collaboration with our Federal, state, local, and international drug regulatory partners. FDA is working diligently to efficiently and effectively use the resources and authorities provided by Congress to protect the public health of the U.S. and to help ensure that imported products are safe for American consumers. Despite the challenges which face us, the American drug supply continues to be among the safest in the world. Thank you for the opportunity to testify. I look forward to responding to any questions you may have.